REMARKS

Specification Amendments

Paragraphs [0070], [0071], [0072], [0074], and [0075] are amended to provide appropriate trademark references for Tissue Tearor, Superscript II, Microcon, GenePix, ImmunoCruz, Triton, and ApoAlert, and to correct minor obvious typographical errors.

Claim Amendments

Claims 1-5, 9-11, 28, 30-40 and 46-59 were in the application. Claims 57 and 58 were withdrawn by the Examiner in the action.

Claims 1, 9, 30, 31, 33, 35, 37, 48 and 55 are now amended. Claims 3, 28, 32, 34, 36, 38-40, 46, 47, 49-51, 53, 54, and 56-59 are now canceled without prejudice. New claims 60-64 are added.

Claims 1, 2, 4, 5, 9-11, 30, 31, 33, 35, 37, 48, 52, 55, and 60-64 are now subject to examination.

Claim 1 is amended to more particularly describe and distinctly claim the invention.

The preamble provides a method for determining if a human has an acute ischemic renal tubular cell injury that can progress to acute renal failure (ARF). Express and inherent support is found in previously-presented and now canceled claim 56, and at paras. [0038], [0045], and [0101].

Method step (a) provides a urine sample obtained from a human within a period of time of about 12 hours after an event that can cause an acute ischemic renal tubular cell injury, and that predisposes the human to progressing to ARF. Ample support, including express and inherent support, is found at paras. [0038], which describes events, and specifically cardiac surgery and kidney transplantation, which predispose the patient to ARF, and at para. [0045], which describe subjects who are "prone to developing ARF". Additional support is found at paras. [0034] and [0100] along with Figure 15 for human kidney transplantation via western blot and ELISA, and at paras. [0035] and [0101] along with Figure 16 for human open heart surgery via western blot and ELISA.

Method step (a) also provides that the event selected from the group consisting of (a) a surgical procedure selected from the group consisting of cardiac surgery, and vascular surgery,

and (b) kidney transplantation. Support is from claim 37. Support for open heart surgery is found in para. [0101].

Method step (d) provides correlating an elevated level of detected antibody-NGAL complex to the human having the acute ischemic renal tubular cell injury that can progress to ARF. In support of the amendment, paragraphs [0034] and [0100] along with Figure 15 in Example 5 demonstrate that increased urinary NGAL associated with renal tubular cell injury, after kidney transplantation, was easily quantified by Western blot and ELISA, and the elevated quantities (levels) correlated with progression to ARF. Paragraphs [0035] and [0101] along with Figure 16 in Example 6 demonstrate that increased urinary NGAL associated with renal tubular cell injury after open heart surgery, was quantified by Western blot and ELISA, and the elevated quantities (levels) correlated with progression to ARF.

Claim 9 is amended to provide antecedent basis for claim 10.

Claim 30 is amended to more particularly describe and distinctly claim the invention.

The preamble provides a method for determining if a mammalian subject has an acute ischemic renal tubular cell injury that can progress to acute renal failure (ARF). Express and inherent support is found in previously-presented and now canceled claim 56, and at paras. [0038], [0045], and [0101].

Method step (a) provides detecting a quantity of NGAL in a urine sample. Ample express and inherent support can be found at paras. [0043] and [0081].

Method step (a) also provides that the urine sample is obtained from a mammalian subject within a period of time of about 12 hours after an event that is suspected of causing an acute ischemic renal tubular cell injury, and that predisposes the mammalian subject to progressing to ARF. Ample support, including express and inherent support, is found at paras. [0038], which describes events, and specifically cardiac surgery and kidney transplantation, which predispose the patient to ARF, and at para. [0045], which describe subjects who are "prone to developing ARF". Additional support is found paras. [0022] and [0089] along with Figure 4B (upper panel) for mice via western blot, at paras. [0024] and [0091] along with Figure 6 for rats via western blot, and at paras. [0035] and [0101] along with Figure 16 for humans via western blot and ELISA.

Method step (b) provides correlating an elevated quantity of NGAL in the urine sample to the mammalian subject having the acute ischemic renal tubular cell injury that can progress to

ARF. Ample support, including express and inherent support, of the correlation of elevated quantities with progression to ARF is found at paras. [0022] and [0089] along with Figure 4B (upper panel) for mice via western blot, at paras. [0024] and [0091] along with Figure 6 for rats via western blot, at paras. [0034] and [0100] along with Figure 15 for human kidney transplantation via western blot and ELISA and at paras. [0035] and [0101] along with Figure 16 for human open heart surgery via western blot and ELISA.

Claim 31 is amended to correct antecedent basis to the quantity of NGAL of claim 30.

Claim 33 is amended to correct antecedent basis to the event of claim 30, and to provide that the obtained urine sample is the first urine output of the subject immediately following the event.

Claim 35 is amended to delete a redundant feature.

Claim 37 is amended to delete as events (c) the administration of nephrotoxic agents, (d) cardiovascular event, and (e) other conditions, to delete "coronary bypass surgery" in the group of surgical procedures, and to add open heart surgery. Express support for open heart surgery is found in para. [0101].

Claim 48 is amended to correct antecedent basis in the elevated level of complex and the acute ischemic renal tubular cell injury that can progress to ARF of claim 1.

Claim 55 is amended to correct antecedent basis in the acute ischemic renal tubular cell injury of claim 31.

New claims 60 and 61 depend from claims 1 and 30, respectively, and provide that the elevated level and quantity of antibody-NGAL complex, respectively, is at least a 10-fold increase in the level of antibody-NGAL complex. Direct support is found in para. [0101] and Figure 16.

New claim 62 depends from claim 1 and provides that the urine sample is an unprocessed urine sample. Support is found in para. [0078].

New claims 63 and 64 depend from claims 35 and 1, respectively, and provide that the period of time (within which the urine sample is obtained) is selected from the group consisting of 3 hours, 2 hours, 1 hour, and 30 minutes. Support is found in the respective claims 35 and 1.

New claim 65 depends from claim 30 and provides that the elevated quantity of NGAL is significantly elevated above a smaller increased quantity of NGAL in a mammalian subject having an acute ischemic renal tubular cell injury that does not progress to ARF. Express support is found in para. [0101] and Figure 16.

Applicants believe the amendments to the claims find full support in the specification, and that no additional claim fees are due.

Priority

The Examiner has denied Applicants' claim for benefit of prior-filed US provisional patent application 60/458,143 (hereinafter, "the Priority Application"), for failing to provide adequate support or enablement in the manner provided by first paragraph of 35 USC 112, for one or more claims of the present application.

Applicants specifically do not agree with the Examiner's previous determination the present application as previously claimed, was not entitled to the claim of priority to the Priority Application.

Nevertheless, for the sake of progressing examination, Applicants request reconsideration of the claim of priority in view of the amendments to Claims 1 and 30 that limit the methods to acute ischemic renal tubular cell injuries, whereby the disclosure of the Priority Application provides more than adequate support and enablement in the manner provided by 35 USC 112, 1st paragraph for one or more claims of the present benefit-claiming application as contemplated by the Examiner.

Objection to the Specification

Applicants thank the Examiner for calling to their attention the necessity of giving appropriate trademark attribution to the products Tissue Tearor, Superscript II, Microcon, GenePix, ImmunoCruz, Triton, and ApoAlert. Such amendments have been made as requested by the Examiner.

Claim Rejections

I. Claims 1-5, 9-11, 30-40, 46-56 and 59 are rejected under 35 USC 112, first paragraph (pages 6-9 of the Action)

A. Claims 37 and 40 are rejected for failing to comply with the written description requirement. (pages 6-8 of the Action)

Without acquiescing to the rejection or its basis, Applicants request withdrawal of the rejection. Claim 37 has been amended to delete the events to sepsis and dehydration. Claim 40 has been canceled.

B. Claims 1-5, 9-11, 30-40, 46-56 and 59 are rejected for failing to enable the *presence* of NGAL with the *presence* of renal tubular cell injury. (pages 8-9 of the Action)

The rejection concludes that the data reported in the specification only support the use of elevated levels of NGAL as an indication of the presence of disease.

The rejection also states that "it is known that disease-free subjects possess detectable levels of urinary NGAL". The Examiner's cites a 2008 publication in support of the rejection. Applicants object to the use of a publication dated almost four years after the filing date should be cited in support of the rejection.

Applicants specifically do not agree with the Examiner's determination that the claims lack enablement, and do not agree that the data reported in the specification only support the use of elevated levels of NGAL as an indication of the presence of disease.

Nevertheless, for the sake of progressing examination, Applicants request reconsideration and withdrawal of the rejection based on the amendments to the claims.

Specifically, Applicants have amended **Claim 1** to provide for determining if a human has an acute ischemic renal tubular cell injury that can progress to acute renal failure (ARF), and to provide for correlating an elevated level of detected antibody-NGAL complex to the human having the acute ischemic renal tubular cell injury that can progress to ARF. **Claim 30** is similarly amended, to provide for determining if a mammalian subject has an acute ischemic renal tubular cell injury that can progress to ARF, and to provide for correlating an elevated quantity of NGAL to the mammalian subject having the acute ischemic renal tubular cell injury that can progress to ARF. **Claim 46** has been canceled.

Applicants have demonstrated that these claims as amended are fully supported by the disclosure as filed, and obviate the Examiner's rejection under 35 USC 112, first paragraph.

II. Claims 37 and 40 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. (pages 9-11 of the Action)

Without acquiescing to the rejection or its basis, Applicants request withdrawal of the rejection. Claim 37 has been amended to delete reference to "coronary bypass surgery", and the events to sepsis and dehydration. Claim 40 has been canceled.

III. Claims 5, 30 and 32-33, 50 and 53 are rejected under 35 USC 103(a) as being obvious over Matthaeus 1 or Matthaeus 2, in view of Gold et al. (US 6,242,246), Ramsden et al. (US 4,640,909), Blaser et al. ("A sandwich enzyme...") and Moses et al. (US 7,153,660) or in the alternative, over either Matthaeus 1 or Matthaeus 2, and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al. (pages 11-17 of the Action)

The Examiner rejects the claims as obvious over a combination of the above 5, or alternatively 6, references.

Without acquiescing to the rejection or its basis, Applicants request reconsideration and withdrawal of the rejection in view of the amendments to the claims, and in view of the following arguments. Rejected claims 32, 50 and 53 have been canceled. Applicants incorporate herein by reference their arguments over this rejection from the response filed November 27, 2007, and provide additional remarks herein after.

(i) Claim 30 has been amended to provide that the urine sample is obtained from the mammalian subject within a period of time of about 12 hours after an event that can cause an acute ischemic renal tubular cell injury, and that predisposes the human or mammalian subject to progressing to ARF; and to provide correlating an elevated quantity of NGAL in the urine sample, to the mammalian subject having the acute ischemic renal tubular cell injury that can progress to ARF.

(ii) At item 49, page 38 of the Action, the Examiner states that "absent evidence of criticality(,) it is maintained that it would have been obvious to sample " 'within 24 hours' out of the course of routine optimization with a reasonable expectation of success given that Matthaeus 1 teach that NGAL was upregulated 'after 24 and 48 hours'".

Applicants traverse this finding in the rejection.

The Examiner's allegation of "routine optimization" does not explain what Matthaeus was attempting to optimize; it is clear that Matthaeus 1 was not attempting to optimize the earliest time by which TIMP-1, MMP-9, and NGAL proteins appeared in the kidney tissue. Applicants assert that whatever optimizing of the sampling time might be done in view of Matthaeus, Applicants claimed range does not overlap or fall inside of the range disclosed by Matthaeus 1. The Examiner has not established that Applicant's claimed range (within 12 hours) and the prior art range (after 24 and 48 hours) are "close enough that one skilled in the art would have expected them to have the same properties". (See MPEP 2144.05, part I). Furthermore, Matthaeus 1 does not discuss or suggest that the timing for taking the kidney sample, or the onset of the appearance of MMP-9, TIMP-1 and NGAL, was of any importance or criticality. The rejection therefore fails to state a *prima facie* case of obviousness.

The Examiner asserts that there was a "reasonable expectation of success" because "Matthaeus 1 teach that NGAL was upregulated 'after 24 and 48 hours'". Applicants can not understand how a person of ordinary skill would consider that Matthaeus provides a reasonable expectation of finding a successful biomarker of renal tubular cell injury based upon the relied-upon teaching of Matthaeus. Indeed, serum creatinine, the only well-established biomarker of impaired renal function, can elevate at 24-48 hours, but is not elevated at less than 12 hours. Applicants believe that rejection lacks a suitable basis or rationale for making the assertion of a "reasonable expectation of success".

(iii) At item 50, page 39 of the Action, the Examiner finds as unpersuasive, Applicants' argument that Mattheaus' choice of method (homogenized kidney tissue) was particularly well-suited for obtaining the sought-after information, since, the Examiner concludes, Matthaeus was also interested in the NGAL protein expression. Applicants concede the fact that Matthaeus was also studying NGAL protein expression; however, Matthaeus was not looking for an early biomarker for the onset of ischemic renal injury itself, or for an injury marker that predicts the progression to ARF. Matthaeus was studying the co-expression of NGAL with MMP-9 and TIMP-1 in response to an ischemic injury, where a sample of the kidney tissue 24 hours after the injury was induced is suitable.

Furthermore, the Examiner bears the burden of showing that the protein expression in the urine would have been obvious. The Examiner supports a finding that it would be obvious to

employ urine as a sample source in Matthaeus, instead of kidney tissue, because isolating kidney tissue is very invasive, and isolating kidney tissue is 'an unsuitable method' for diagnosing renal injury in humans. This assertion is, however, without basis or support in the absence of the teaching of Applicants' own invention.

Without considering Applicants' claimed invention, a person of ordinary skill would have found that isolating kidney tissue (either excising portions or homogenizing the whole kidney) was entirely necessary and appropriate for the purposes of Matthaeus' study, that being to observe the pattern and location of mRNA and protein expression in a post-ischemic kidney. The invasiveness of a method depends on the context of its use. For the purpose identified in Matthaeus 1 of studying the synthesis and expression of NGAL, MMP-9 and TIMP-1, a person of ordinary skill would find isolating kidney tissue entirely appropriate and non-invasive.

Furthermore, Mattheaus 1 says that NGAL protein expression was upregulated after 24 and 48 hours, and that immunocytochemistry of NGAL revealed bright fluorescence in the most extensively damaged areas, which is stated to be the "injured proximal tubuli". Applicants believe that a person of ordinary skill would understand that these findings by the authors of Matthaeus 1 could not have been determined if urine sampling were substituted for the methodology of Matthaeus. Therefore, for the purposes taught in Matthaeus 1, urine sampling is not an obvious substitution for the method of isolating kidney tissue disclosed in Matthaeus 1 (or Matthaeus 2).

Applicants also rebut here any finding of a "reasonable expectation of success", because a person of ordinary skill in the art would understand that there are thousands of proteins expressed in the kidney at any time, and a similar number of proteins expressed in an injured kidney, yet nearly all of these proteins never appear in the urine.

The Examiner therefore has not provided sufficient rationale to overcome the burden of proof of showing that a person of ordinary skill would find it obvious to use urine as another method, instead of homogenized or excised kidney tissue.

(iv) Even if the 5 or 6 references cited in the rejection were to be combined as suggested in the rejection (which Applicants otherwise dispute), none of the references individually or collectively teach that the elevated quantity of NGAL detected in the urine sample within 12 hours of the injury-causing event can be correlated with an acute ischemic renal tubular cell

injury that can progress to acute renal failure. Matthaeus 1 and 2 do not describe that an elevated quantity of NGAL in the urine correlates with an acute ischemic injury that can progress to ARF.

Ohlsson et al. does not disclose acute, ischemic injuries to the kidneys, and does not teach or suggest a correlation of an amount of NGAL (in urine) to an acute ischemic injury that can progress to ARF. It is also noted that Ohlsson et al. published in March 2003, and more specifically it has been determined that Ohlsson et al. has a publication date of March 1, 2003. The attached Devarajan 131 Declaration, which is discussed in detail *supra* on page 20 of this Response with regard to the Muramatsu reference, establishes that the claimed invention was made prior to the effective date of the Ohlsson et al reference, such that the Ohlsson et al reference is not prior art against the claimed invention. The rejection in view of Ohlsson et al then should be withdrawn.

None of Gold et al, Ramsden et al, Blaser et al, or Moses et al disclose acute, ischemic injuries to the kidneys, or teach or suggest a correlation of an amount of NGAL (in urine) to an acute ischemic injury that can progress to ARF. Blaser describes collecting the urine samples of healthy donors over a 24 hour period, and mixing the samples together prior to analysis, which appears to teach away from detecting NGAL in the urine as a time-dependent biomarker. (See the last sentence in section 2.4 *Preparation of the samples*, on page 139). Consequently, the rejection should be withdrawn.

Claim 5 depends from claim 30.

Claim 33 as amended to provide that the obtained urine sample is the first urine output of the subject immediately after the event. Applicants believe that there is no express or inherent disclosure in any one or combination of references that disclose or suggest this feature of the invention.

Claims 32, 50 and 53 are canceled.

IV. Claims 1, 4, 9-11, 28, 31, 34-36, 39-40, 46-47, 49 and 54-56 are rejected under 35 USC 103(a) as being obvious over Matthaeus 1 or 2, in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al.; or alternatively Matthaeus 1 or 2 in view of Ohlsson et al, Gold et al., Ramsden et al., Blaser et al. and Moses et al., -- and further in view of David et al. (US 4,376,110) (pages 17-20 of the Action)

Without acquiescing to the rejection or its basis, Applicants request reconsideration and withdrawal of the rejection in view of the amendments to the claims, and in view of the following arguments. Rejected claims 28, 34, 36, 39-40, 46-47, 49, 54 and 56 have been canceled. Claims 1, 4, 9-11, 31, 35, and 55, and new claims 60 and 61 remain under examination. Applicants incorporate herein by reference their arguments over this rejection from the response dated November 26, 2007, as well as the arguments hereinabove with respect to Matthaeus 1 and 2, and the other references.

The present independent Claims 1 and 30, to which claim 31 depends, have been amended to provide that the urine sample is obtained from the human or mammalian subject within a period of time of about 12 hours after an event that can cause an acute ischemic renal tubular cell injury, and that predisposes the human or mammalian subject to developing ARF, the event being selected from the group consisting of (a) a surgical procedure selected from the group consisting of open heart surgery, cardiac surgery, and vascular surgery, and (b) kidney transplantation; and to provide correlating an elevated level of detected antibody-NGAL complex or NGAL in the urine sample, to the human or mammalian subject having the acute ischemic renal tubular cell injury that can progress to ARF.

Even if the 6 or 7 references were to be combined as suggested in the rejection (which Applicants would otherwise dispute), none of the references individually or collectively teach that the quantity or level of NGAL detected in the urine sample within 12 hours of the injury-causing event can be correlated with an acute ischemic renal tubular cell injury that can progress to acute renal failure. Matthaeus 1 and 2, Ohlsson et al, Gold et al, Ramsden et al, Blaser et al, or Moses et al are discussed, supra. David et al does not disclose acute, ischemic injuries to the kidneys, and does not teach or suggest a correlation of a level of NGAL (in urine) to an acute ischemic injury that can progress to ARF. David et al. does teach a rapid and sensitive assay for detecting analytes in fluids. David et al does not make, contrary to the rejections assertion, any teaching or suggestion that would motivate a person of ordinary skill to obtain a sample from a subject earlier in time after an event that causes an injury, than that time already taught in the art. Matthaeus 1 and 2 make no disclosure that would suggest to a person of ordinary skill that the kidney tissue should be sampled at an earlier time, within 24 hours.

Since the combination of references does not disclose or suggest each feature of the claim(s), the rejection does not state a *prima facie* obviousness rejection, and should be withdrawn as against claims 1 and 31, and claims depending therefrom, including claim 55.

Claim 35 provides that the period of time (within which the urine sample is obtained after the event) is selected from 6 hours, 4 hours, 3 hours, 2 hours, 1 hour, and 30 minutes. Applicants believe that there is no express or inherent disclosure in any one or combination of references that disclose or suggest this feature of the invention.

Claims 28, 34, 36, 39-40, 46-47, 49, 54 and 56 are canceled.

V. Claim 2 is rejected under 35 USC 103(a) as being obvious over Matthaeus 1 or 2 in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus 1 or 2 and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al. -- and further in view of Valkirs et al. (US 2003/0109420) (page 20-21 of the Action)

The Examiner rejects the claim as obvious over Matthaeus 1 or 2 and/or Ohlsson et al., in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., previously addressed, in view of Valkirs et al.

Matthaeus 1 and 2, Ohlsson et al, Gold et al, Ramsden et al, Blaser et al, or Moses et al are discussed, supra. Without acquiescing to the rejection or its basis, Applicants request reconsideration and withdrawal of the rejection in view of the amendments to the claims, and in view of the preceding arguments.

VI. Claim 2-3 are rejected under 35 USC 103(a) as being obvious over Matthaeus 1 and 2 in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus 1 and 2, and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., -- and further in view of Linzer et al. (US 3,635,091) (page 21-22 of the Action)

The Examiner rejects claim 2 and 3 as obvious over Matthaeus 1 or 2 and/or Ohlsson et al., in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., previously addressed, further in view of Linzer et al.

Matthaeus 1 and 2, Ohlsson et al, Gold et al, Ramsden et al, Blaser et al, or Moses et al are discussed, supra. Without acquiescing to the rejection or its basis, Applicants request reconsideration and withdrawal of the rejection with respect to claim 2 in view of the amendments to claim 30, and in view of the preceding arguments. Claim 3 has been canceled.

VII. Claim 33-38 and 59 are rejected under 35 USC 103(a) as being obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., -- and further in view of Muramutsu. (Kidney International) (page 22-24 of the Action)

The Examiner rejects claims 33-38 and 59 as obvious over Matthaeus 1 or 2 and/or Ohlsson et al., in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., previously addressed, further in view of Muramatsu et al.

Matthaeus 1 and 2, Ohlsson et al, Gold et al, Ramsden et al, Blaser et al, or Moses et al are discussed, supra.

Muramatsu et al has a publication date of November, 2002.

Without acquiescing to the rejection or its basis, Applicants request withdrawal of the rejection on the ground that the Muramatsu et al reference is not prior art against the claimed invention.

Applicants take the position that Muramatsu et al. is being asserted as prior art under 35 USC 103(a) as a 102(a) reference, having published less than one year prior to the earliest priority application pertaining to Applicants' claimed invention.

Applicants present herewith a Declaration under 37 CFR 1.131 by co-inventor Prasad Devarajan that demonstrates conception, and reduction to practice, of the claimed invention in the United States, prior to the effective date of the Muramatsu reference.

The showing of facts made in the Declaration should be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application. Original exhibits of drawings or records, or photocopies thereof, must accompany and form part of the affidavit or declaration or their absence must be satisfactorily explained.

The Muramatsu et al reference has an unspecified effective date in November 2002.

The Devarajan 131 Declaration demonstrates the conception and reduction to practice of the invention as claimed, prior to November 1, 2002 in the United States. More specifically, the Devarajan 131 Declaration describes an experiment that showed the conception and reduction to practice of a method for determining if a mammal has an acute ischemic renal tubular cell injury that can progress to ARF. The experiment provided a mammal on which a surgical procedure event was performed. The surgical procedure was suspected of causing an acute ischemic renal tubular cell injury that predisposed the mammal to progressing to ARF. The experiment included obtaining urine samples from the mammal within a period of time of 12 hours after the surgical event, and described a western blot assay to identify the quantities of lipocalin (NGAL) protein in the obtained urine samples. The experiment also showed that the elevated quantities of NGAL correlated with the later progression of the mice to ARF at 24 hours, as evidenced by the elevated levels of plasma creatinine at 24 hours.

The Devarajan 131 Declaration establishes that the claimed invention was made prior to the effective date of the Muramatsu reference, such that the reference is not prior art against the claimed invention. The rejection should be withdrawn.

VIII. Claims 47-48 and 55 are rejected under 35 USC 103(a) as being obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., Moses et al., and David -- and further in view of Kosako et al. (page 24-25 of the Action)

The Examiner rejects claim 47, 48 and 55 as obvious over Matthaeus 1 or 2 and/or Ohlsson et al., in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., previously addressed, further in view of Kosako et al.

Matthaeus 1 and 2, Ohlsson et al, Gold et al, Ramsden et al, Blaser et al, or Moses et al are discussed, supra.

Without acquiescing to the rejection or its basis, Applicants request reconsideration and withdrawal of the rejection in view of the amendments to the claims, and in view of the preceding arguments. Of the claim rejection, claims 47 has been canceled. Claims 48 and 55 remains under examination.

IX. Claim 51 is rejected under 35 USC 103(a) as being obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., -- and further in view of Madsen et al and Calvet et al. (page 25-26 of the Action)

The rejection is rendered moot by cancellation of claim 51.

X. Claim 52 is rejected under 35 USC 103(a) as being obvious over Matthaeus et al. in view of Gold et al., Ramsden et al., Blaser et al. and Moses et al., or in the alternative, Matthaeus et al. and Ohlsson et al. in view of Gold et al., Ramsden et al., Blaser et al., and Moses et al., -- and further in view of Brady et al. (page 26-27 of the Action)

Applicants traverse.

Brady et al discusses the processing of biological samples starting at paragraph [0082].

[0082] "Subject biological materials assayed using the present method may be unprocessed (e.g.,, urine, serum or plasma) or processed. A primary goal of processing is the solubilization of the sample.

[0083] Where the biological material is a tissue, it is usually de-fatted by two brief extractions (e.g., 15 min.) with acetone or chloroform:methanol (2:1 v/v). Mineralized tissues are, for example, powdered under liquid nitrogen and subsequently demineralized using extraction with 0.5 M EDTA at pH 7.5 for 72-96 hours at 4° C. Connective tissue samples are typically denatured by heating the sample in saline at pH 7.4 for 30 min at 70° C.

A person of ordinary skill in the art would understand that the term "unprocessed" in Brady refers to body samples that are already fluids or "homogenized". Brady identifies urine, serum and plasma as unprocessed fluids *per se*, because that they do not need processing to render them homogenized. The "process" in Brady is "homogenization". Brady does not mention specifically an "unprocessed urine sample", and does not distinguish between a urine sample that is "unprocessed" and a urine sample that is "processed", such as by centrifugation.

Applicants' description describes urine samples that are centrifuged to remove debris, as mentioned in paragraph [0076], which is understood by a person of ordinary skill to be a well known means of processing a urine sample. A person of ordinary skill in the art knows, equally as well, that an unprocessed urine sample is as-is or as sampled, without centrifugation or some

other process. Therefore, Brady does not teach preparation or use of an unprocessed urine sample in an assay, as claimed by Applicants.

XI. Double Patenting (Pages 27-32)

(i) Co-pending Application No. 11/096,113 (attorney docket CHM-025M)

Claims 1-5, 9-11, 28, 30-40, 46-56 and 59 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over the claims 2, 4, 7-10 and 22-39 of co-pending Application No. 11/096,113 (Applicants' commonly-owned, co-pending application, attorney docket CHM-025M), in view of Ramsden et al, Blaser et al. and Moses et al. Co-pending Application No. 11/096,113 has claims related to detecting NGAL in a sample of blood to identify if the subject is predisposed to progressing to acute renal failure as a result of an acute renal tubular cell injury.

Applicants respectfully request reconsideration and withdrawal of the double patenting rejection, for the following reasons.

In the record of later-filed, co-pending and commonly-invented Application No. 11/096,113, Applicants have established that, while NGAL appeared in the urine from an acute ischemic renal injury, NGAL was not found in renal vein of the acute ischemic kidney, and have stated that a person of ordinary skill in the art who induced an ischemic injury to the kidney would not have found NGAL in the renal vein, and would have had no expectation of finding NGAL in the circulating blood system.

Ramsden et al. teach only the very general concept of urine sampling as a non-invasive sampling means. Blaser et al. disclose detection of NGAL in urine of only healthy donors. Moses et al. teach to a person of ordinary skill in the art, detection of MMP, and more particularly complexes of MMP-9 with NGAL, in urine, in patients with cancer.

Consequently, NGAL in the urine and NGAL in the blood are from distinct sources, and represent two separate and distinct pools of NGAL. The urine NGAL assay of the present application would not provide a reasonable expectation of success in developing the blood NGAL assay of the reference application 11/096,113. Therefore, the claims of the reference application 11/096,113 are not obvious over the instant claims, and the claims of the instant application are not obvious over the reference application 11/096,113 in view of Ramsden et al., Blaser et al, and Moses et al.

(ii) Co-pending Application No. 11/770,422 (attorney docket CHM-015C)

Claims 1-5, 9-11, 28, 30-40, 46-56 and 59 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over the claims 2, 4, 7-10 and 22-39 of co-pending Application No. 11/770,422 (Applicants' commonly-owned, co-pending application, attorney docket CHM-015C), in view of David et al. Co-pending application No. 11/770,422 is a continuation of the present application.

Applicants intend to file a Terminal Disclaimer in the first of the present application and the reference application no. 11/770,422 that has allowed claims.

(iii) Co-pending Application No. 11/770,372 (CHM-025MC)

Claims 1-5, 9-11, 28, 30-40, 46-56 and 59 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over the claims 2, 4, 7-10 and 22-39 of co-pending Application No. 11/770,372 (Applicants' commonly-owned, co-pending application, attorney docket CHM-025MC), in view of David et al, Ramsden et al., Blaser et al. and Moses et al.

Co-pending Application No. 11/770,372 is a continuation of application No. 11/096,113 (attorney docket CHM-025M) discussed above.

Applicants respectfully request reconsideration and withdrawal of the double patenting rejection, for the reasons stated above.

(iv) Co-pending Application No. 11/770,214 (CHM-032A3)

Claims 1-5, 9-11, 28, 30-40, 46-56 and 59 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over the claims 2, 4, 7-10 and 22-39 of co-pending Application No. 11/770,214 (commonly-owned, co-pending application, attorney docket CHM-032A3), in view of David et al. Co-pending application no. 11/770,214 has claims related to detecting NGAL in a sample of urine obtained from a subject having a chronic renal injury.

Applicants request reconsideration and withdrawal of the provisional restriction requirement, on the basis that the claims of the present application are drawn to acute renal tubular cell injuries, whereas the claims of the reference application 11/770,214 are drawn to chronic renal tubular cell injuries. The acute and chronic injuries are generally caused by

different types of events or diseases, and the Examiner has not identified any reference or line of reasoning which would demonstrate to a person of ordinary skill in the art that an effective biomarker for acute renal injury would be also an effective biomarker for chronic renal tubular cell injury.

(v) Co-pending Application No. 11/770,245 (CHM-032B3)

Claims 1-5, 9-11, 28, 30-40, 46-56 and 59 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over the claims 2, 4, 7-10 and 22-39 of co-pending Application No. 11/770,245 (Applicants' commonly-owned, co-pending application, attorney docket CHM-032B3), in view of David et al, Ramsden et al., Blaser et al. and Moses et al.

Co-pending application no. 11/770,245 has claims related to detecting NGAL in a sample of blood obtained from a subject having a chronic renal injury. Applicants respectfully request reconsideration and withdrawal of the double patenting rejection, for the reasons stated above related to application No. 11/096,113 (attorney docket CHM-025M).

CONCLUSION

Applicants believe a full and complete response to the Action has been made, and that the claims are patentable over the prior art of reference. Applicants request a prompt notice of allowance of the application.

Respectfully submitted,

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By _____

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